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EXAMINER	
SAJJADI, FEREYDOUN GHOTB	
ART UNIT	**PAPER NUMBER**
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/502,235	KISIELOW ET AL.	
	Examiner	Art Unit	
	Fereydoun G. Sajjadi	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23* is/are pending in the application.

4a) Of the above claim(s) *13 and 21-23* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12, 14-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the papers filed October 21, 2005. Applicant's response to restriction requirement of October 5, 2005 has been entered. No claims were amended or withdrawn. Currently, claims 1-23 are pending in the application.

Election/Restrictions

Applicant's election of Group I (claims 1-12 and 14-20), without traverse, drawn to a method of expressing a desired isoform of a gene in a mammalian cell, comprising the introduction into said cell, of at least a partially double stranded (ds) RNA having at least 95% sequence identity to a common sequence shared by two or more isoforms of said gene and introducing into said cell a vector expressing the said desired isoform of a gene; and a kit comprising reagents that include the said ds RNA and said vector for said method, is acknowledged. Applicant's species election of tumor suppressive (claim 12) and MCF-7 cell line (claim 15) by a subsequent oral communication is also acknowledged. Claims 13 and 21-23 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Because Applicant did not traverse the requirement for election, the election requirement is maintained and hereby made final.

Information Disclosure Statement

The information disclosure statement filed 10/19/2004 fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. It has been placed in the application file, but the information referred to therein has not been fully considered, since several references were not present in the instant application. Applicant is required to provide copies of the missing references to be considered by the examiner.

Claim Objections

Claim 1 objected to because of the following informalities: the preamble of claim 1 is inconsistent with the body of the claim. The preamble recites a method of expressing a desired isoform

of a gene product in a cell, i.e. any type of cell. However, the body of the claim recites a mammalian cell. Appropriate correction of the preamble to recite a mammalian cell is required.

Claim 11 is dependent on claim 1 and also requires correction to recite a mammalian cell.

Claim Rejections - 35 USC § 112-Indefinite

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 16 and 20 are rejected under 35 USC § 112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as his invention.

Claim 1 is unclear. The claim recites a method of expressing a desired isoform of a gene product in a cell absent undesired isoforms of a gene product. It is not clear what is meant by a cell absent undesired isoforms of a gene product, because the "undesired" is relative in meaning, and further, does not specify what exactly is the material or structure of "isoforms" that renders them undesirable. It is further unclear whether the undesired isoforms of a gene product pertain to the same gene encoding the desired isoform. Claim 20 is similarly unclear.

Claim 16 is unclear. The claim recites the method of claim 1, wherein said desired isoform is transcribed under the control of an endogenous promoter. It is not clear whether said endogenous promoter is present in an expression vector containing said desired isoform (i.e. being the same promoter in an expression vector as recited in claim 1), or whether said desired isoform is introduced in the proximity of an endogenous promoter in a cell.

Claim Rejections - 35 USC § 112, Written Description

The following is a quotation of the first paragraph of 35 U.S.C. §112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-12 and 14-20 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The claim(s) contain(s) subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art (hereafter the Artisan), that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1 and 20 read on a method of expressing a desired isoform of a gene product in a cell wherein the undesired isoforms of said gene product are absent, comprising introducing into said cell a ds RNA having at least 95% sequence identity to a common nucleic acid sequence shared by two or more isoforms of said gene product. As such, claim 1 requires knowledge of a sizable number of isoforms of any gene products that may be expressed as multiple isoforms, in order to determine which isoforms of a gene product would be considered undesired. Further, the claim requires knowledge of numerous desired isoforms of a gene product, whether endogenous to said cell or isoforms that may be exogenous in origin. Knowledge of numerous isoforms would also be required to determine the nature of the sequences that would constitute a common and shared nucleic acid.

Claim 11 is drawn to the method of claim 1, wherein said desired isoform replaces a mutant isoform in the cell. Claim 12 is drawn to the method of claim 11, wherein the undesired mutant isoform is tumor suppressive.

The specification defines isoform "to encompass gene products that are produced as a result of differential gene splicing as well as from the use of alternative transcription start sites. In addition, ...the term isoforms include any closely related sequences and therefore may include a mutated gene in a cell" (p. 10, lines 30-31, bridging p. 11, lines 1-4). The specification discloses the Shc gene family as exemplary for isoforms of a signaling adaptor/scaffold gene product (Example 1, p. 17) with ShcA, as exemplary for the desired isoform (line 6, p.18) and specifically describe the use of 21-mer oligonucleotide pairs as siRNAs of Shc (lines 28-29, p. 18). However, the specification provides no description of the substantial number of genes that can express more than one isoform, as claimed in claims 1 and 20. The specification is further devoid of any description for a desired isoform replacing a mutant isoform or a tumor suppressive mutant isoform in a cell. Moreover, Applicant's specification provides no description of additional desired isoforms endogenous to a cell or any isoforms that may be exogenous in origin. Claims 1 and 20 encompasses a large number of genes and gene products, whose expression can give rise to more than one isoform and all exogenous related nucleic acid

sequences that may constitute a desired isoform of a gene. Claim 1 and 20 thus constitute a claimed genus that represents other genes and gene products, yet to be discovered, and since the specification only describes a specific type of gene family, namely Shc, the disclosed species do not constitute a substantial portion of the claimed genus. As such, the Artisan of skill could not predict that Applicant possessed any additional species of devices or incompatible components. Hence, only the direct injection catheter could be demonstrated as possessed.

To satisfy the written description requirement, a patent specification must describe the claimed invention in sufficient detail such that the Artisan can reasonably conclude that the inventor(s) had possession of the claimed invention. Such possession may be demonstrated by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and/or formulae that fully set forth the claimed invention. Possession may be shown by an actual reduction to practice, showing that the invention was "ready for patenting", or by describing distinguishing identifying characteristics sufficient to show that Applicant was in possession of the claimed invention (January 5, 2001 Fed. Reg., Vol. 66, No. 4, pp. 1099-11). Moreover, MPEP 2163 states:

> [A] biomolecule sequence described only by a functional characteristic, without any known or disclosed correlation between that function and the structure of the sequence, normally is not a sufficient identifying characteristic for written description purposes, even when accompanied by a method of obtaining the claimed sequence.

Applicant's attention is also directed to *In re Shokal*, 113 USPQ 283 (CCPA 1957), wherein it is stated:

> It appears to be well settled that a single species can rarely, if ever, afford sufficient support for a generic claim. *In re Soll*, 25 CCPA (Patents) 1309, 97 F2d 623, 38 USPQ 189; *In re Wahlforss*, 28 CCPA (Patents) 867, 117 F2d 270, 48 USPQ 397. The decisions do not however fix any definite number of species which will establish completion of a generic invention and it seems evident therefrom that such number will vary, depending on the circumstances of particular cases. Thus, in the case of small genus such as the halogens, consisting of four species, a reduction to practice of three, perhaps even two, might serve to complete the generic invention, while in the case of a genus comprising hundreds of species, a considerably larger number of reductions to practice would probably be necessary.

Overall, what these statements indicate is that the Applicant must provide adequate description of such core structure and function related to that core structure such that the Artisan of skill could determine the desired effect. Hence, the analysis above demonstrates that Applicant has not determined the core structure for full scope of the claimed genus.

In analyzing whether the written description requirement is met for genus claims, it is first determined whether a representative number of species have been described by their complete structure. Therefore, the breadth of the claims as reading on all incompatible components of all medical devices that are yet to be discovered; in view of the level of knowledge or skill in the art at the time of the invention, an Artisan of skill would not recognize from the disclosure that Applicant was in possession of the genus of numerous genes and gene products that may give rise to or be described as isoforms (claims 1 and 20) and a sizable number of desired isoforms of a gene that may be endogenous or exogenous to a cell, or a replacement of a mutant isoform in a cell with a desired isoform. Thus it is concluded that the written description requirement is not satisfied for the claimed genus. Claims 2-12 and 14-19 depend from claim 1.

In sum, this limited information is not deemed sufficient to reasonably convey to one skilled in the art that Applicant is in possession of a representative number of desired or undesired isoforms (including mutant undesired isoforms, that include tumor suppressive) of genes, at the time the application was filed. Thus it is concluded that the written description requirement is not satisfied for the claimed genus.

Claim Rejections - 35 USC § 112-Scope of Enablement

Claims 1-13 and 14-20 are rejected under 35 U.S.C.§112, first paragraph, because the specification, while being enabling for a method expressing a desired isoform of the Shc gene product in a mammalian cell *in vitro,* following suppression of the expression of the undesired isoforms of said gene product, by contacting said cell with ds RNA, does not reasonably provide an enablement for a method of expressing a desired isoform of any gene product in a cell absent undesired isoforms of any gene product (claims 1 and 20), by exposing said cell to dsRNA, and wherein said cell is a cancer cell (claim 14), as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

In determining whether Applicant's claims are enabled, it must be found that one of skill in the art at the time of invention by Applicant would not have had to perform "undue experimentation" to make and/or use the invention claimed. Factors to be considered in determining whether a disclosure

meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404:

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

MPEP § 2164.04 states: "[W]hile the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection."

The Nature Of The Invention And Breadth Of Claims

Claim 1 is drawn to a method of expressing a desired isoform of a gene product in a cell absent undesired isoforms of a gene product, said method comprising: (a) exposing a mammalian cell to at least one nucleic acid, said nucleic acid having at least 95% sequence identity to a common nucleic acid sequence shared by two or more isoforms of said gene product; and (b) introducing an expression vector encoding a desired isoform of said gene product into said mammalian cell. Claims 2-12 and 14-19 depend from claim 1. Claim 14 further limits the method of claim 1, wherein said cell is a cancer cell. Claim 20 is drawn to a kit comprising reagents for practicing the method of claim 1. When given their broadest reasonable interpretation, in view of the as filed specification, claims 1, 14 and 20 encompass methods of expressing a desired isoform of a gene product both *in vitro* and *in vivo*, by procedures that involve delivery of nucleic acids to cells other than direct contact (aerosol delivery for instance) and for applications that may include gene therapy (claim 14 for example). The specification teaches that the mammalian cell can be any cell of interest (line 17, p. 11); and that the desired isoform may be transcribed as a transgene *in vivo*, either as si/dsRNA or in the form of a hairpin structure. The specification additionally envisions the use of the isoform for correction of aberrant isoforms, in a method for treating disease in a subject by various pharmaceutical compositions (pp. 15-17).

The detail of the disclosure provided by Applicant, in view of the prior art, must encompass a wide knowledge, so that the Artisan of skill would be able to practice the invention as claimed by

Applicant, without undue burden being imposed on such Artisan. This burden has not been met because it would require undue experimentation to suppress the expression of undesired isoforms of any gene product and additionally promote the expression of any desired gene product *in vivo*, by various routes of delivery that encompass exposing a cell to a nucleic acid and for applications such as gene therapy, as claimed in claim 1, 14 and 20 of the instant application.

The Unpredictability Of The Art And The State Of The Prior Art

The invention is in a class of invention which the CAFC has characterized as "the unpredictable arts such as chemistry and biology." Mycogen Plant Sci., Inc. v. Monsanto Co., 243 F.3d 1316, 1330 (Fed. Cir. 2001).

The state of the prior art with regard to regulation of gene expression by RNAi is effectively summarized by the references of Muller, U. (Mechanisms of Dev. 82:3-21, 1999, of record); Tuschl et al. (U. S. Patent Application No.: 2004/0259247, filed Nov. 29, 2001); and Kisielow et al. (Biochem. J. 363:1-5, 2002, of record).

The art teaches that double-stranded RNA (ds RNA) induces sequence- specific post-transcriptional gene silencing by a process known as RNA interference (RNAi), mediated by short 19-23 nucleotide RNA fragments, having overhanging 3' ends, in a Drosophila *in vitro* system (Tuschl et al., Abstract). The prior art also teaches rescue by complementation or reverse genetics, employed for proof that a specific mutated phenotype may be reverted to wild type by reintroducing a functional gene copy or various mutants of said gene (Muller, p. 13, column 1, under 3.3). However, the art does not teach the isoform-specific expression of any gene mediated by RNAi *in vivo*, or by numerous modes of nucleic acid delivery.

Claims 1, 14 and 20 of the instant application are drawn to a method of expressing a desired isoform of a broad genus of all genes encoding isoforms or whose products are modified to constitute isoforms, comprising various methods of nucleic acid delivery and under numerous conditions, including *in vivo*, for applications that may include gene therapy, not apparent from the disclosure of the invention. The instant specification provides for the inhibition of the expression of Shc gene family isoform products in HeLa tissue culture cells, *in vitro* (Example 1, p. 17) as exemplary for a gene family expressing desired and undesired isoforms of a gene, and further describe the isoform specific knockdown of said isoforms by transfection with sequence specific siRNA Example 2, p.20), and

isoform specific expression of ShcA by transfection of HeLa cells with an expression vector containing the mutated form of the ShcA gene, as exemplary for the expression of a desired isoform (Example 3, pp. 21-25). Because exposing a cell to a nucleic acid would entail numerous methods of nucleic acid delivery, including viral, particle mediated or by aerosol administration, and further, to any mammalian cell type *in vitro* or *in vivo*, it would require undue experimentation by the skilled Artisan to carry out tests on all mammalian cell types, including living cells, and to further test the various modes of gene delivery, as claimed in claims 1, 14 and 20.

The unpredictability of attenuating expression of a target gene in all types of cells, including mammalian cells, by RNA interference (RNAi) is evident in prior and post-filing art. While it is recognized that introduction of dsRNA that is targeted to a specific gene may result in attenuation of expression of the targeted gene, the degree of attenuation and the length of time that attenuation is achieved is not predictable. Caplen et al. (Gene 2000, vol. 252, p.95-105) provide evidence of the unpredictability of dsRNA attenuation of a targeted gene in vertebrate cells *in vitro*. Caplen et al. report that although dsRNA inhibits gene expression in cultured *Drosophila* cells, screening of three commonly used cell lines from three different species: human, hamster, and mouse, using cells expressing transgenes both transiently and permanently, produced mixed results.

RNA interference is recognized in the art as not enabled for therapeutic purposes. Caplen (Expert Opin. Biol. Ther. 2003, v. 3(4): 575-586) points out that, even post filing in 2003, "Many of the problems associated with developing RNAi as an effective therapeutic are the same as encountered with previous gene therapy approaches. The key issues of delivering nucleic acids to the required tissue and cell type, while ensuring an appropriate level of efficacy with minimum toxicity induced by the vector system...". (see page 581) Those of skill in the art of RNA interference are optimistic about the potential of RNA interference as a therapeutic tool, but even with the advances made subsequent to the filing of the instant application, the field recognizes that therapeutic methods are not yet effective. Thus, the post-filing art clearly suggests that administering dsRNA, either *in vitro* or *in vivo*, to attenuate expression of target genes is not a reproducible or predictable art.

Given these teachings, the skilled artisan would not know *a priori* whether introduction of dsRNA or hairpin nucleic acids into any type of cell, either *in vivo* or *in vitro*, by the broadly disclosed methodologies of the instant invention, would result in successful attenuation/inhibition of a target gene. One of skill in the art would not know how to deliver dsRNA or hairpin nucleic acids to an

organism in such a way that would ensure an amount sufficient to attenuate expression of a target gene is delivered to the proper cell.

In fact, the state of the art is such that successful delivery of nucleotide sequences to a target cell *in vivo* or *in vitro*, such that the oligonucleotide provides the requisite biological effect to the target cells/tissues/organs, must be determined empirically. Methods of inhibiting gene expression using nucleic acids *in vivo* are unpredictable with respect to delivery of the nucleic acid molecule such that the nucleic acid molecule is targeted to the appropriate cell/organ, at a bioeffective concentration and for a period of time such that the nucleic acid molecule is effective in, as in the instant application, attenuating or inhibiting expression of a target gene such that the organism exhibits a loss of function phenotype.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of dsRNA for use in RNA interference in various types of cells and in the therapeutic application of RNAi in any mammal, including humans. The field of RNA interference does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

In order to practice the claimed invention *in vivo* a number of variables would have to be optimized, including 1). the mode of delivery of the oligonucleotide to an organism that would allow it to reach the targeted cell, 2). the amount of oligonucleotide that would need to be delivered in order to allow inhibition of the expression of a target gene once it reached the proper cell and 3). ensuring the oligonucleotide remains viable in a cell for a period of time that allows inhibition of the gene to an extent that there is a measurable and significant therapeutic effect. Each one of these variables would have to be empirically determined for each dsRNA or hairpin nucleic acid.

It is further noted that, the specification in the instant application does not teach how an expression vector encoding a desired isoform of a gene can be used effectively in administering transgene either via numerous possible routes of delivery or to a multitude of mammalian cells *in vivo* or *ex vivo*. The specification also does not provide any guidance as to how studies in HeLa tissue culture cells can be extrapolated to other cell types or human situations. In addition, prior art at the time of filing of this application as described *supra*, does not provide any convincing guidance in this regard either. The cited art clearly indicates an unpredictable status for the practice of gene therapy pertaining to the regulation of gene expression.

In view of the lack of teachings or guidance provided by the specification with regard to all methods of nucleic acid delivery to a mammalian cell, and the lack of teachings or guidance provided by the specification to overcome the difficulties and unpredictability of gene delivery *in vivo*, and for the specific reasons cited above, it would have required undue experimentation for an Artisan of skill to make and use the claimed invention. Hence, absent a strong showing by Applicant, in the way of specific guidance and direction, and/or working examples demonstrating the same, such invention as claimed by Applicant is not enabled.

The Amount Of Direction Or Guidance Presented And Working Examples

The specification fails to disclose adequate representations of desired isoforms of all gene products, all methods of nucleic acid delivery to a cell and conditions required for *in vivo* gene delivery. The specification discloses the three isoforms of the Shc gene and a combination of RNAi and plasmid mediated gene expression for transfection in HeLa cells *in vitro* (Examples 1-3, pp. 17-25). However, the specification provides no additional examples of isoforms of a gene product. Moreover, Applicant's specification provides no examples of gene delivery other than plasmid mediated by transfection and no examples of RNA interference other than transfection in tissue culture. The guidance provided by the specification amounts to an invitation for the skilled Artisan to try and follow the disclosed instructions to make and use the claimed invention. The specification merely discloses the inhibition and subsequent expression of an isoform of a Shc gene product *in vitro* following transfection of HeLa cells.

Quantity Of Experimentation

The quantity of experimentation in this area is extremely large, as there are a significant number of parameters, which would have to be studied and tested to make and definitively show that one is in possession of the multitude isoforms of a representative number of genes genes, numerous methods and modes of gene delivery to a cell and *in vivo* expression of a desired isoform of a gene for gene therapy. This would require a significant degree of inventive effort, with each of the many intervening steps, upon effective reduction to practice, not providing any guarantee of success in the succeeding steps.

Level Of Skill In The Art

The level of skill in the art at the time of invention is deemed to be high. However, because of the immaturity of the art, and its unpredictability, as shown by the other factors, one of skill in the art at the time of invention by Applicant would not have been able to make and/or use the invention claimed without undue experimentation.

Analysis And Summary

Applicant is therefore enabled for a method expressing a desired isoform of the Shc gene product in a mammalian cell *in vitro,* following suppression of the expression of the undesired isoforms of said gene product by RNAi, and subsequent introduction of a mutant form of the desired isoform of the Shc gene by transfection *in vitro*. In the instant case, as discussed above, in a highly unpredictable art where the identification and analysis of numerous isoforms of a large number of gene products and conditions required for various modes of gene delivery to numerous mammalian cells in settings that include *in vivo,* together with the large quantity of research required to define these unpredictable variables, and the lack of guidance provided in the specification, it is the position of the examiner that it would require undue experimentation for one of skill in the art to perform the method of the claim as broadly written.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C.§102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-12 and 14-20 are rejected under 35 USC § 102(e) by Tuschl et al. (U. S. Patent Application No.: 2004/0259247, filed Nov. 29, 2001).

Claim 1 recites a method of expressing a desired isoform of a gene product in a cell absent undesired isoforms of a gene product, said method comprising (a) exposing a mammalian cell to at

least one nucleic acid, said nucleic acid being at least a partially double-stranded ribonucleic acid and the double-stranded portion having at least 95% sequence identity to a common nucleic acid sequence shared by two or more isoforms of said gene product; and (b) introducing an expression vector encoding a desired isoform of said gene product into said mammalian cell, said desired isoform having a sequence comprising one or more mismatches relative to said double-stranded portion of said nucleic acid, operably linked to a promoter capable of driving expression of said desired isoform in said cell. Claim 2 limits the common nucleic acid sequence to at least 19 consecutive nucleotides in length, and claims 3 and 4 confine the common nucleic acid sequence to all endogenous isoforms and the double stranded portion of said nucleic acid to 100% sequence identity to said common nucleic acid sequence. Claim 20 is drawn to a kit comprising reagents that enable the method of claim 1.

Tuschl et al. teach 19-23 nucleotide short double stranded RNA that induce post-transcriptional gene silencing by a process known as RNA interference (RNAi). Chemically synthesized short interfering RNAs (siRNA) duplexes with overhanging 3' ends mediate efficient target cleavage (Abstract). Tuschl et al. demonstrate the mechanisms of RNAi using *in vitro* lysates, in addition to Drosophila Schneider S2 cells and mammalian HeLa cells, with luciferase genes serving as targets of gene silencing (Paragraphs [0094-0095], column 1, p. 7; and Example 2, p. 12). They further teach "Gene-specific knockout phenotypes of cells ...may be used in analytic procedures, e.g. in the functional and /or phenotypical analysis of gene expression profiles and/or proteomes. For example, one may prepare the knock-out phenotypes of human genes in cultured cells which are assumed to be regulators of alternative splicing processes" (paragraph [0036, column 2, p. 3). "Using RNAi based knockout technologies, the expression of an endogenous target gene may be inhibited in a target cell" (paragraph [0037], column 2, p. 3), further, "capable of inhibiting the expression of at least one endogenous target gene or with a DNA encoding at least one double stranded RNA molecule capable of inhibiting the expression of at least one endogenous target gene. It should be noted that the present invention allows a target-specific knockout of several different endogenous genes due to the specificity of RNAi" (paragraph [0035], column 2, p. 3). "The endogenous gene may be complemented by an exogenous target nucleic acid coding for the target protein or a variant or mutated form of the target protein, e.g. a gene or a cDNA" (paragraph [0038], column 2, p. 3).

Applicant should be note that exogenous and endogenous target genes described by Tuschl et al. are equivalent to desired and undesired isoforms of a gene product respectively, as the exogenous

target nucleic acid is encoding the endogenous target protein, and hence is capable of complementation. As stated by Tuschl et al. the complementation may be achieved by an exogenous target nucleic acid coding for the endogenous gene; i.e. the endogenous and exogenous target nucleic acids have identical sequences (the limitation of claim 10).

Tuschl et al. further teach that: "Variants or mutated forms of the target gene differ from the endogenous target gene in that they encode a gene product which differs from the endogenous gene product on the amino acid level by substitutions, insertions and/or deletions of single or multiple amino acids. The variants or mutated forms may have the same biological activity as the endogenous target gene" (paragraph [0038], column 1, p. 4). "The complementation may be accomplished by coexpressing the polypeptide encoded by the exogenous nucleic acid...This coexpression may be achieved by using a suitable expression vector...Proteins and protein complexes which are synthesized de novo in the target cell will contain the exogenous gene product....In order to avoid suppression of the exogenous gene product expression by the RNAi duplex molecule, the nucleotide sequence encoding the exogenous nucleic acid may be altered on the DNA level (with or without causing mutations at the amino acid level) in the part of the sequence which is homologous to the double-stranded RNA molecule." (paragraph [0039, column 1, p. 4). Therefore, the common double stranded portion of Tuschl et al. may be 100% identical to the common nucleic acid sequence. The silent alterations in the sequence of the exogenous nucleic acid taken together with the amino acid substitutions stated *supra*, comprise the two or more mismatch limitations of claim 7, the at least one codon difference limitation of claim 8 and the two codon differences of claim 9.

Further, "the system as described above preferably comprises: (d) at least one exogenous target nucleic acid coding for the target protein or a variant or mutated form of the target protein wherein said exogenous target nucleic acid differs from the endogenous target gene on the nucleic acid level such that the expression of the exogenous target nucleic acid is substantially less inhibited by the double stranded RNA molecule than the expression of the endogenous target gene" (paragraphs [0049 and 0050], column 2, p. 4). Therefore, Tuschl et al. effectively anticipate all the limitations of claim 1-4 and 20.

Claim 5 is drawn to a method of claim 1, wherein said nucleic acid is 19 to 25 nucleotides long. Tuschl et al. describe Fig. 16 wherein "the antisense siRNA was the same in all siRNA duplexes, but the sense strand was varied between 18 to 25 nt by changing the 3'end" (paragraph [0086], column 1,

p. 7). Tuschl et al. also describe experiments in HeLa cells wherein "double-stranded RNA molecules having a length of preferably from 19-25 nucleotides have RNAi activity. Thus, in contrast to the results from *Drosophila* also 24 and 25 nt long double-stranded RNA molecules are efficient for RNAi (paragraph [0007], column 2, p. 1). Figure 19 teaches "Variation of the length of siRNA duplexes with preserved 2-nt 3' overhangs" (paragraph [0090], column 2, p. 7), thus anticipating the limitation of claim 6.

Claim 11 is directed to the method of claim 1, wherein said desired isoform replaces a mutant isoform in the cell. Tuschl et al teach that "the variant or mutated target gene may also have a biological activity which differs from the biological activity of the endogenous target gene, e.g. a partially deleted activity, a completely deleted activity, an enhanced activity, etc." (paragraph [0038], bridging, column 1, p. 4). Further stating: "In an especially preferred embodiment, an analysis of a variant or mutant form of one or several target proteins is carried out, wherein said variant or mutant forms are reintroduced into the cell or organism by an exogenous target nucleic acid as described above" (paragraph [0040], column 1, p. 4).

Claim 12 depends form claim 11 and further limits claim 11 to a mutant isoform that is tumor suppressive. Tuschl et al. teach: "The target gene to which the RNA molecule of the invention is directed may be associated with a pathological condition. For example, the gene may be ...a tumor-associated gene" (paragraph [0030], column 1, p.3). A tumor suppressive gene is also considered a tumor-associated gene.

Claims 14 and 15 are directed to the method of claim 1, wherein the cell is a cancer cell or an MCF-7 breast cancer cell respectively. Tuschl et al. teach: "The method of the invention may be used for determining the function of a gene in a cell...capable of mediating RNA interference. The cell is preferably a eukaryotic cell or a cell line, e.g. a plant cell or an animal cell, such as a mammalian cell, ...a tumor cell, e.g. ...a teratocarcinoma cell" (paragraph [0029], column 1, p. 3). A tumor cell line reads on a cancer cell and the MCF-7 cancer cell line.

Claims 16-19 are drawn to the method of claim 1, wherein the desired isoform is expressed under the control of endogenous, constitutive, inducible and tissue-specific promoters respectively. Tuschl. et al. teach that complementation may be achieved by coexpression "using a suitable expression vector" (paragraph [0039], column 1, p. 4) and further describe expression vectors with SV40 (constitutive) and HSV TK (inducible) regulatory elements (paragraph [0070], column 1, p. 6),

they do not specifically teach desired isoforms or target genes under the control of endogenous, and tissue-specific promoters. However, at the time of the instant invention, the expression of transfected genes in expression vectors under the control of said promoters or regulatory elements, or any suitable promoter sequence was considered routine in the art.

Conclusion

Claims 1-12 and 14-20, not allowable.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst William Phillips, whose telephone number is **(571) 272-0548**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fereydoun G. Sajjadi whose telephone number is **(571) 272-3311**. The examiner can normally be reached Monday through Friday, between 7:00 am-4:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dave T. Nguyen can be reached on **(571) 272-0731**. The fax phone number for the organization where this application or proceeding is assigned is **(571) 273-8300**. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989).

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